Amendments to the Specification

Please amend Paragraph 25 in the following manner:

[0025] These and other benefits of the invention are achieved by directly targeting absorption by the papillary dermis and by controlled delivery of drugs, diagnostic agents, and other substances to the dermal space of skin. The inventors have found that by specifically targeting the intradermal space and controlling the rate and pattern of delivery, the pharmacokinetics exhibited by specific drugs can be unexpectedly improved, and can in many situations be varied with resulting clinical advantage. Such **pharmacokinetics** ~~**pharmacokeneties**~~ cannot be as readily obtained or controlled by other parenteral administration routes, except by IV access.

Please replace Paragraph 26 with the following replacement paragraph (*i.e.*, the text of Paragraph 26 as originally filed):

[0026] The present invention improves the clinical utility of ID delivery of drugs, diagnostic agents, and other substances to humans or animals. The methods employ dermal-access means (for example a small gauge needle, especially microneedles), to directly target the intradermal space and to deliver substances to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the dermal-access means within the dermis provides for efficacious delivery and pharmacokinetic control of active substances. The dermal-access means is so designed as to prevent leakage of the substance from the skin and improve adsorption within the intradermal space. The pharmacokinetics of hormone drugs delivered according to the methods of the invention have been found to be vastly different to the pharmacokinetics of conventional SC delivery of the drug, indicating that ID administration according to the methods of the invention will provide improved clinical results. Delivery devices that place the dermal-access means at an appropriate depth in the intradermal space and control the volume and rate of fluid delivery provide accurate delivery of the substance to the desired location without leakage.

Please amend Paragraph 30 in the following manner:

[0030] Figure 1 shows a timecourse of plasma insulin levels of intradermal versus subcutaneous bolus administration of fast-acting **insulin**.

Please amend Paragraph 39 in the following manner:

[0039] The dermal-access means used for ID administration according to the invention is not critical as long as it penetrates the skin of a subject to the desired targeted depth within the intradermal space without passing through it. In most cases, the device will penetrate the skin **[[and]]** to a depth of about 0.5-2 mm. The dermal-access means may comprise conventional injection needles, catheters or microneedles of all known types, employed singularly or in multiple needle arrays. The dermal-access means may comprise needleless devices including ballistic injection devices. The terms "needle" and "needles" as used herein are intended to encompass all such needle-like structures. The term microneedles as used herein **is [[are]]** intended to encompass structures smaller than about 30 gauge, typically about 31-50 gauge when such structures are cylindrical in nature. Non-cylindrical structures **encompassed** ~~**encompass**~~ by the term microneedles would therefore be of comparable diameter and include pyramidal, rectangular, octagonal, wedged, and other geometrical shapes. Dermal-access means also include ballistic fluid injection devices; **[[,]]** powder-jet delivery devices; **[[,]]** piezoelectric, electromotive, **and** electromagnetic assisted delivery devices; **and [[,]]** gas-assisted delivery devices, **all** of which directly penetrate the skin to provide access for delivery or directly deliver substances to the targeted location within the dermal space. By varying the targeted depth of delivery of substances by the dermal-access means, pharmacokinetic and pharmacodynamic (PK/PD) behavior of the drug or substance can be tailored to the desired clinical application most appropriate for a particular patient's condition. The targeted depth of delivery of substances by the dermal-access means may be controlled manually by the practitioner, or with or without the assistance of indicator means to indicate when the desired depth is reached. Preferably however, the device has structural means for controlling skin penetration to the desired depth within the intradermal space. This is most typically accomplished by means of a widened area or hub associated with the shaft of the dermal-access means that may take the form of a

backing structure or platform to which the needles are attached. The length of microneedles as dermal-access means are easily varied during the fabrication process and are routinely produced in less than 2 mm length. Microneedles are also **[[a]]** very sharp and of a very small gauge, to further reduce pain and other sensation during the injection or infusion. They may be used in the invention as individual single-lumen microneedles or multiple microneedles may be assembled or fabricated in linear arrays or two-dimensional arrays as to increase the rate of delivery or the amount of substance delivered in a given period of time. Microneedles may be incorporated into a variety of devices such as holders and housings that may also serve to limit the depth of penetration. The dermal-access means of the invention may also incorporate reservoirs to contain the substance prior to delivery or pumps or other means for delivering the drug or other substance under pressure. Alternatively, the device housing the dermal-access means may be linked externally to such additional components.

Please amend Paragraph 50 in the following manner:

[0050] Substances that can be delivered intradermally in accordance with the present invention are intended to include pharmaceutically or biologically active substances including ~~include~~ diagnostic agents, drugs, and other substances which provide therapeutic or health benefits such as for example nutraceuticals. Diagnostic substances useful with the present invention include macromolecular substances such as, for example, inulin, ACTH (e.g. corticotropin injection), luteinizing hormone-releasing hormone (**e.g. [[eg.]]**, Gonadorelin Hydrochloride), growth hormone-releasing hormone (e.g. Sermorelin Acetate), cholecystokinin (Sincalide), parathyroid hormone and fragments thereof (e.g. Teriparatide Acetate), thyroid releasing hormone and analogs thereof (e.g. protirelin), secretin and the like.

Please amend Paragraph 56 in the following manner:

[0056] in which E_{max} is the maximal stimulation of k_{out} by insulin, EC_{50} is the insulin concentration at which stimulation of k_{out} is half maximal, C is the concentration of insulin, and γ is the Hill coefficient of the relationship. Initial modeling efforts utilized the plasma concentration of insulin as the mediator of pharmacologic response. However, this approach did not capture the delay in response of plasma glucose to increasing concentrations of plasma

insulin. Therefore, an effect-compartment modeling approach was finally adopted in which the effect of insulin was mediated from a hypothetical effect compartment peripheral to the systemic pharmacokinetic compartment.

Please amend Paragraph 67 in the following manner:

[0067] Bolus delivery of Lilly Lispro fast acting insulin was performed using ID and SC bolus administration. The ID injection microdevice was dermal access array design SS3_34. 10 international insulin units (U) corresponding to 100 uL volume respectively, were administered to diabetic Yucatan Mini swine. Test animals had **[[been]]** previously been rendered diabetic by chemical ablation of pancreatic islet cells, and were no longer able to secrete insulin. Test animals received their insulin injection either via the microneedle array or via a standard 30 G X ½ in. needle inserted laterally into the SC tissue space. Circulating serum insulin levels were detected using a commercial chemiluminescent assay kit (Immulite, Los Angeles, CA) and blood glucose values were determined using blood glucose strips. ID injections were accomplished via hand pressure using an analytical microsyringe and were administered over approximately 60 sec. By comparison, SC dosing required only 2-3 sec. Referring to Figure 1, it is shown that serum insulin levels after bolus administration demonstrate more rapid uptake and distribution of the injected insulin when administered via the ID route. The time to maximum concentration (T_{max}) is shorter and the maximum concentration obtained (C_{max}) is higher for ID vs. SC administration. In addition, Figure 2 also demonstrates **that** the pharmacodynamic biological response to the administered insulin, as measured by the decrease in blood glucose (BG), showed faster and greater changes in BG since more insulin was available early after ID administration.

Please amend Paragraph 69 in the following manner:

[0069] Lilly Lispro is regarded as fact acting insulin, and has a slightly altered protein structure relative to native human insulin. **[[.]]** Hoechst regular insulin **[[,]]** maintains the native human insulin protein structure that is chemically similar, but has slower uptake than Lispro when administered by the traditional SC route. Both insulin types were administered in bolus via the ID route to determine if any differences in uptake would be discernable by

this route. 5U of either insulin type were administered to the ID space using dermal access microdevice design SS3_34. The insulin concentration verses time data shown in Figure 3. When administered by the ID route the PK profiles for regular and fast-acting insulin were essentially identical, and both insulin types exhibited faster uptake than Lispro given by the traditional SC route. This is evidence that the uptake mechanism for ID administration is less affected by minor biochemical changes in the administered substance, and that ID delivery provides an advantageous ~~advantagous~~ PK uptake profile for regular insulin that is superior to SC administered fast-acting insulin.

Please amend Paragraph 71 in the following manner:

[0071] Bolus delivery of Lilly Lispro fast-acting insulin via microneedle arrays having needles of various lengths was conducted to demonstrate that the precise deposition of drug into the dermal space is necessary to obtain the PK advantages and distinctions relative to SC. Thus, 5U of Lilly Lispro fast-acting insulin was administered using dermal access design SS3_34. Additional microdevices of the same needle array configuration were fabricated whereby exposed needle lengths of the microdevice array were lengthened to include arrays with needles lengths of 2 and 3 mm. The average total dermal thickness in Yucatan Mini swine ranges from 1.5-2.5 mm. Therefore insulin deposition is expected to be into the dermis, approximately at the dermal/SC interface, and below the dermis and within the SC for 1mm, 2mm, and 3mm length needles respectively. Bolus insulin administration was as described in EXAMPLE II. **[[.]]** Average insulin concentrations verses time are shown in Figure 4. The data clearly **[[shows]]** **show that** as microneedle length is increased, the resulting PK profile begins to more closely resemble SC administration. **The** **[[This]]** data **demonstrate** ~~demonstrates~~ the benefits of directly targeting the dermal space**;** **[[,]]** such benefits include rapid uptake and distribution, and high initial concentrations. Since the data are averages of multiple examples, they do not show the increased inter-individual variability in PK profiles from longer 2 and 3mm microneedles. **The** **[[This]]** data **demonstrate** ~~demonstrates~~ that since skin thickness may vary both between individuals and even within a single individual, shorter needle lengths that accurately target the dermal space are more reproducible in their PK profile since they are depositing the drug more consistently in the same tissue

compartment. **The [[This]]** data **demonstrate that** ~~**demonstrates**~~ longer microneedles that deposit or administer substances deeper into the dermal space, or partially or wholly into the SC space, mitigate or eliminate the PK advantages in comparison to shallow, directly targeted administrations to the highly vascularized dermal region.

Please amend Paragraph 75 in the following manner:

[0075] Bolus ID delivery of human granulocyte colony stimulating factor (GCSF) (Neupogen) was administered via dermal access microdevice designs SS3_34B (array) or SS1_34 (single needle) to Yucatan minipigs. Delivery rate was controlled via a Harvard syringe pump and was administered over a 1-2.5 min period. Figure 6 shows the PK availability of GCSF in blood plasma as detected by an ELISA immunoassay specific for GCSF. Administration via IV and SC delivery was performed as controls. Referring to Figure 6, bolus ID delivery of GCSF shows the more rapid uptake associated with ID delivery. C_{max} is achieved at approximately 30-90 minutes vs. 120 min for SC. Also the bioavailability is dramatically increased by an approximate factor of 2 as evidenced by the much higher area under the curve (AUC). Circulating levels of GCSF are detectable for an extended period, **indicating** ~~**indicting**~~ that ID delivery does not alter the intrinsic biological clearance mechanism or rate for the drug. These data also show that device design has minimal effect on the rapid uptake of drug from the ID space. The data referred to in Figure 7 also **show [[shows]]** the degree and time course of white blood cell expansion as a result of GCSF administration with respect to a negative control (no GCSF administered). White blood cell (WBC) counts were determined by standard cytometric clinical veterinary methods. ID delivery exhibits the same clinically significant biological outcomes. Although all delivery means give approximately equal PD outcomes, **the [[this]]** data **suggest** ~~**suggests**~~ ID delivery could enable use **of** half the dose to achieve essentially the same physiological result in comparison to SC, due to approximately 2-fold bioavailability increase.